



## MEMORANDUM

DATE:

FROM: Director, Office of Science, Center for Tobacco Products, FDA

TO: Tobacco Products Scientific Advisory Committee (TPSAC)

SUBJECT: April 18 Meeting of the Tobacco Products Scientific Advisory Committee (TPSAC)

Thank you for your participation in the upcoming meeting of the TPSAC.

This meeting will provide the opportunity for the Center for Tobacco Products (CTP) to elicit comments from the TPSAC and the public regarding the evaluation of modified risk tobacco product applications.

Per Section 911(f), FDA will be referring MRTPAs to TPSAC for recommendations. Therefore, in preparation for the time when TPSAC will be presented with the complexity associated with the evaluation of a MRTPA, FDA seeks discussion by TPSAC on various issues related to this complexity and the reliance on indirect evidence in the assessment of modified risk tobacco product applications. At the meeting of the Committee on April 18, FDA will pose questions related to whether TPSAC has any recommendations for FDA about how the agency should deal with scientific information from a variety of sources when evaluating modified risk tobacco product applications; whether TPSAC believes FDA should have greater concern for any particular sources of scientific information, i.e., indirect evidence, during the evaluation of an MRTPA; whether particular sources of information should be weighed more heavily during the evaluation of an MRTPA; and if TPSAC has any recommendations for addressing areas of concern after the issuance of an order to market a modified risk tobacco product.

Summary of Briefing Package Contents:

- Evaluation of Modified Risk Tobacco Product Applications – Background Information from FDA
- Draft Guidance to Industry on Modified Risk Tobacco Applications

We look forward to seeing you on April 18th.

## **Evaluation of Modified Risk Tobacco Product Applications**

### **Background**

The Food, Drug and Cosmetic Act (FD&C Act) defines “modified risk tobacco product” as any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products. [Section 911(b)(1)]. Sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products means a tobacco product

- (1) that represents in its label, labeling, or advertising, either implicitly or explicitly, that:
  - i. the tobacco product presents a lower risk of tobacco-related disease or is less harmful than one or more other commercially marketed tobacco products;
  - ii. the tobacco product or its smoke contains a reduced level of a substance or presents a reduced exposure to a substance; or
  - iii. the tobacco product or its smoke does not contain or is free of a substance;
- (2) that uses the descriptors “light”, “mild”, “low”, or similar descriptors in its label, labeling, or advertising;<sup>1</sup> or
- (3) for which the tobacco product manufacturer has taken any action directed to consumers through the media or otherwise, other than by means of the tobacco product’s label, labeling, or advertising, after June 22, 2009, respecting the product that would be reasonably expected to result in consumers believing that the tobacco product or its smoke may present a lower risk of disease or is less harmful than one or more commercially marketed tobacco products, or presents a reduced exposure to, or does not contain or is free of, a substance or substances. [Section 911(b)(2)]

The modified risk tobacco product provisions of the FD&C Act may be valuable tools in the effort to protect public health by reducing the morbidity and mortality associated with tobacco use, particularly if companies take advantage of these provisions by making bold, innovative product changes that substantially reduce, or even eliminate altogether, either the toxicity or addictiveness of tobacco products, or both. However, the U.S. experience with the marketing of “light” cigarettes - cigarettes purporting lower levels of exposure to carbon monoxide, tar and

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<sup>1</sup> While cigarettes had been marketed with such descriptors before the Tobacco Control Act was enacted, as of June 22, 2010, manufacturers were prohibited from manufacturing for sale or distribution any tobacco products for which the label, labeling, or advertising contains the descriptors “light,” “low,” or “mild,” or any similar descriptor, without an FDA order in effect under section 911(g) of the FD&C Act. Section 911(b)(3) of the FD&C Act. Furthermore, as of July 22, 2010, manufacturers, including importers of finished tobacco products, were prohibited from introducing into the domestic commerce of the United States any tobacco product for which the label, labeling, or advertising contains the descriptors “light,” “low,” or “mild,” or any similar descriptor, irrespective of the date of manufacture, without an FDA order in effect under section 911(g) of the FD&C Act. *Id.*

nicotine - demonstrates the potential for the marketing of modified risk tobacco products to increase the likelihood of initiation among non-users of tobacco products and decrease the likelihood of cessation among current users of tobacco products. The statute requires that persons who want to market modified risk tobacco products in interstate commerce first submit a modified risk tobacco product application (MRTPA) to FDA that contains information about various aspects of the tobacco product, including information to enable FDA to assess the likely impacts of an MRTP on individual health outcomes and population-level outcomes, such as rates of initiation or cessation of tobacco product use. FDA has also published for public comment a Draft Guidance to Industry that describes possible studies that could be conducted in order to support an application to market a modified risk tobacco product which will enable FDA to assess of the product's impact on the health of individuals and the population as a whole.

FDA anticipates that MRTPAs will contain a substantial amount of scientific information from a variety of scientific investigations. Data taken from these investigations will be used by FDA to evaluate the potential impact of marketing a proposed modified risk tobacco product on the population. This evaluation will occur prior to the actual marketing of such a product as a modified risk tobacco product. A great deal of complexity is inherent with evaluations that infer the potential impacts of products from studies conducted under conditions that may differ in at least some ways from the actual conditions that may occur once the product is marketed to the general U.S. population. FDA must carefully assess the limitations of certain types of scientific evidence in an MRTPA in order to be able to determine whether the statutory standard for issuing an order authorizing a modified risk tobacco product has been met.

With respect to impacts on the individual, the scientific evidence in an MRTPA is expected to address the likelihood of harm (i.e., tobacco-related disease) from use of the MRTP. For some tobacco products, long-term epidemiological data may exist. For other tobacco products for which long-term epidemiological data do not exist, information may be gleaned from other studies, such as prospective studies to assess the potential impact of a tobacco product on the health of individuals and the potential impact of marketing of the product on the use of the product in the population as a whole. Although FDA recommends that industry provide evidence of impacts on all of the various sub-groups of the U.S. population, the data in an

application may not provide direct evidence of the impacts of marketing of modified risk tobacco products on all of the various types of individuals that comprise the U.S. population. In those cases, FDA will need to draw inferences or extrapolate from the data to assess potential impacts on individuals. For example, there may be cases where existing epidemiological data has been collected from individuals in populations from other regions of the world, which would necessitate drawing inferences from the data to predict potential outcomes in individuals within the U.S. population. Furthermore, there may be other cases where FDA may need to rely on indirect evidence in order to assess the impact of a modified risk tobacco product. These cases are discussed in greater detail later in this document, but examples include the evidence that relates to the levels of exposure posed to users of a tobacco product, or the behaviors that are likely to occur – such as the amount and frequency of use of a product by an individual, the likelihood of adoption of the product by current users of tobacco products, the likelihood of initiation of tobacco product use among non-users, or the likelihood of cessation among current tobacco users that would have otherwise quit using tobacco in the absence of the marketing of the modified risk tobacco product.

On April 18, 2014, FDA requests that the members of the TPSAC convene to discuss approaches for evaluating the scientific information that FDA anticipates to receive in MRTPAs. FDA will pose questions to the TPSAC to obtain recommendations about how FDA could approach certain issues related to the complexity of scientific information in MRTPAs, particularly with drawing inferences from indirect evidence of the potential impacts of modified risk tobacco products on individual and population health.

Section 911(g) of the FD&C Act describes the demonstrations applicants must make to obtain an order from FDA. Sections 911(g)(1) and (2) of the FD&C Act set forth two bases for FDA to issue an order.

In general, FDA shall issue an order under section 911(g)(1) of the FD&C Act (risk modification order) only if it determines the applicant has demonstrated that the product, as it is actually used by consumers, will:

- Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and
- Benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.

FDA has the authority to require with respect to tobacco products for which risk modification orders are issued that the product comply with requirements relating to advertising and promotion of the tobacco product. Section 911(h)(5) of the FD&C Act.

In the alternative, FDA may issue an order under section 911(g)(2) of the FD&C Act (exposure modification order) if it determines that the applicant has demonstrated that:

- Such an order would be appropriate to promote the public health;
- Any aspect of the label, labeling, and advertising for the product that would cause the product to be a modified risk tobacco product is limited to an explicit or implicit representation that the tobacco product or its smoke does not contain or is free of a substance or contains a reduced level of a substance, or presents a reduced exposure to a substance in tobacco smoke;
- Scientific evidence is not available and, using the best available scientific methods, cannot be made available without conducting long-term epidemiological studies for an application to meet the standards for obtaining an order under section 911(g)(1); and
- The scientific evidence that is available without conducting long-term epidemiological studies demonstrates that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies.

Furthermore, for FDA to issue an exposure modification order, FDA must also find that the applicant has demonstrated that:

- The magnitude of the overall reductions in exposure to the substance or substances, which are the subject of the application is substantial, such substance or substances are harmful, and the product as actually used exposes consumers to the specified reduced level of the substance or substances;
- The product as actually used by consumers will not expose them to higher levels of other harmful substances compared to the similar types of tobacco products then on the market unless such increases are minimal and the reasonably likely overall impact of use of the product remains a substantial and measurable reduction in overall morbidity and mortality among individual tobacco users;
- Testing of actual consumer perception shows that, as the applicant proposes to label and market the product, consumers will not be misled into believing that the product is or has been demonstrated to be less harmful or presents or has been demonstrated to present less of a risk of disease than one or more other commercially marketed tobacco products; and

- Issuance of the exposure modification order is expected to benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.

In making determinations under both sections 911(g)(1) and (g)(2) of the FD&C Act, FDA must take into account:

- The relative health risks the modified risk tobacco product presents to individuals;
- The increased or decreased likelihood that existing tobacco product users who would otherwise stop using such products will switch to using the modified risk tobacco product;
- The increased or decreased likelihood that persons who do not use tobacco products will start using the modified risk tobacco product;
- The risks and benefits to persons from the use of the modified risk tobacco product compared to the use of smoking cessation drug or device products approved by FDA to treat nicotine dependence; and
- Comments, data, and information submitted to FDA by interested persons.

What follows is a discussion of the areas where FDA may need to rely on indirect evidence in order to evaluate the potential benefit to health of individuals and of the population as a whole.

### **The Evaluation of the Relative Health Risks to Individuals of an MRTP**

For products seeking an order under Section 911(g)(1), the evidence submitted in an MRTPA has to demonstrate that the tobacco product significantly reduces harm and the risk of tobacco-related disease to individual tobacco users. Applicants might seek to demonstrate this through inference from a combination of studies, such as long-term epidemiological studies, that show or indicate the potential for a causal relationship between use of the tobacco product and health outcomes. However, these demonstrations may in some cases provide only indirect evidence of the impact of modified risk tobacco products and there may be a need to extrapolate the information from studies to determine possible impacts on individuals when the product is marketed as an MRTP. Examples of when this need may arise could include: investigations where individuals participating in the studies may not be representative of the U.S. population, or where there may be insufficient numbers (if any) of individuals from certain sub-populations related to age, gender, ethnicity or race, pre-existing health conditions, or tobacco use behavior; where the individuals in the studies may use the product in environments that differ significantly

from the U.S. marketplace, i.e., the studies may have been conducted outside of the United States or in highly controlled clinical settings; or where the individuals in the studies may use the product differently than individuals in the marketplace, particularly when exposed to MRTP advertising or promotion, e.g., there may be differential effects of MRTP advertising causing certain people to perceive the MRTP as “safe”, which could lead to use of the MRTP at levels much greater than those observed in scientific investigations, or to perceive the product as palliative, which could encourage dual use of the MRTP with other tobacco products.

For products seeking an order under Section 911(g)(2), the evidence submitted in an MRTPA has to demonstrate that a tobacco product poses lower levels of exposure to harmful substances. Applicants might seek to demonstrate this through inference from a combination of studies, such as chemical and toxicological analyses, actual use studies, and clinical trials, that show that use of the product substantially reduces the exposure to one or more substances, that those substances are indeed harmful, that consumers use the product in a manner that reduces the exposure to those substances, and that the reduction will likely be shown, in future studies, to lead to lower rates of tobacco-related harm and disease. Similar to what is anticipated in applications for products seeking an order under Section 911(g)(1), these demonstrations may in some cases rely on indirect evidence of the impact of modified risk tobacco products and there may be a need to extrapolate from the study data to determine possible impacts on individuals when the product is marketed as an MRTP. Examples of when this need may arise could include investigations which measure the impact of the tobacco product on biomarkers of exposure that may not be uniquely related to tobacco use; which measure the impact on biomarkers which have not yet been validated as indicators of tobacco-related disease; which show a great amount of variation in exposure within and between individuals from actual use of the tobacco product; or for products which reduce constituents for which there is not a well-established dose response relationship such that determining whether there is substantial reduction for the constituents could be difficult.

### **The Evaluation of Impacts on Initiation and Cessation of Tobacco Product Use**

Although FDA expects a certain degree of complexity associated with the evaluation of the evidence (both direct and indirect) on health outcomes in individuals, it is likely that, for the

many products with sufficient evidence to support a risk modification or an exposure modification order, the greatest degree of complexity will be associated with the evaluation of the evidence on behavioral effects, i.e., the impacts that the marketing of the product may have on initiation and cessation of tobacco product use.

The evidence submitted in an MRTPA should allow FDA to assess whether the intended users of product (e.g., existing users of other tobacco products who are not likely to quit tobacco use) are likely to adopt the product; whether individuals will use the product such that it reduces harm (e.g., switching from a potentially more harmful tobacco product rather than using the product in conjunction with other tobacco products); and whether non-users (including former users) of tobacco products are likely to initiate use of the tobacco product. Applicants might seek to demonstrate this from a combination of studies, such as the long-term epidemiological studies, clinical studies, and actual use studies already discussed, as well as studies of consumer perception and comprehension of modified risk information.

However, as stated earlier, these investigations may in some cases provide only indirect evidence of the impact of modified risk tobacco products and there may be a need to extrapolate information from studies to determine possible impacts on individual behaviors when the product is marketed as an MRTP. Examples of the when this need may arise have already been discussed, such as investigations where individuals participating in the studies may not be representative of the U.S. population, or where studies may not include sufficient numbers (if any) of individuals from certain sub-populations related to age, gender, ethnicity or race, pre-existing health conditions, or tobacco use behavior; or where the individuals in the studies may use the product in environments that differ significantly from the U.S. marketplace, i.e., the studies may have been conducted outside of the United States or in highly controlled clinical settings; and the individuals in the studies may use the product differently than individuals in the marketplace, particularly when exposed to MRTP advertising or promotion, e.g., there may be differential effects of MRTP advertising causing certain people to perceive the MRTP as “safe”, which could encourage the perception that the product is palliative or which could encourage dual use of the MRTP with other tobacco products. Additional layers of complexity may arise because there may not be direct evidence on the impacts on the likelihood of adoption, initiation,



and cessation due to issues of measurement, e.g., validated measures of consumer perception and other self-reported outcomes and their relation to initiation of tobacco use; to tobacco product type, e.g., in some cases the product may be a novel product for which no prior marketing information exists; and differential impacts of MRTP advertising or promotion on sub-populations within the U.S., such that MRTP adoption or initiation differs by age, gender, ethnicity or race, pre-existing health conditions, or tobacco use behavior.

## **Conclusion**

MRTPAAs will likely contain substantial amount of scientific information from a variety of scientific investigations. Depending on the type of scientific investigation and the hypotheses tested within these investigations, FDA will likely have to make inferences from indirect evidence to evaluate the impacts of the marketing of modified risk tobacco products on the population. .

Despite the complexity of the task of evaluating MRTPAAs due to the numerous factors described earlier, FDA must use the available scientific evidence to make a determination about whether it is appropriate to issue an order to allow a tobacco product to market as a modified risk tobacco product. After FDA has made an evaluation of the various types of impacts discussed above, the agency must make an assessment of the totality of evidence and the likely overall impact of the marketing of a modified risk tobacco product on the health of population as a whole. The overall assessment may rely on the extrapolation of information from indirect evidence on the impact of the population as a whole. During this assessment, FDA may need to place greater weight on certain types of evidence than others. For example, FDA may place greater weight on the data from certain types of studies or from studies that include certain types of individuals.

Even after the issuance of an order authorizing the marketing of a modified risk tobacco product, there may remain areas of concern about the potential long-term impacts of the product once it is allowed to market. In particular, FDA will need to monitor the potential for unintended impacts on tobacco use behavior, e.g., excessive initiation by non-users (including former users) or unforeseen health impacts in certain types of individuals. Thus, on-going post-market surveillance, both active and passive, of modified risk tobacco products will likely be needed to

monitor the impacts of these products on the health of individuals and of the population as a whole and to ensure the continued accuracy of the determinations upon which the marketing order was based.

### **Proposed Topics for Discussion**

Per Section 911(f), FDA will be referring MRTPAs to TPSAC for recommendations. Therefore, in preparation for the time when TPSAC will be presented with the complexity associated with the evaluation of a MRTPA, FDA seeks discussion by TPSAC on various issues related to this complexity and the reliance on indirect evidence in the assessment of modified risk tobacco product applications. At the meeting of the Committee on April 18, FDA will pose questions related to whether TPSAC has any recommendations for FDA about how the agency should deal with scientific information from a variety of sources when evaluating modified risk tobacco product applications; whether TPSAC believes FDA should have greater concern for any particular sources of scientific information, i.e., indirect evidence, during the evaluation of an MRTPA; whether particular sources of information should be weighed more heavily during the evaluation of an MRTPA; and if TPSAC has any recommendations for addressing areas of concern after the issuance of an order to market a modified risk tobacco product.